UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

22-April-2002

MEMORANDUM:

SUBJECT: **Tebuthiuron.** Preliminary Human Health Risk Assessment. HED Chapter for the Tolerance Reassessment Eligibility Decision (TRED). Chemical No. 105501. DP Barcode D274580.

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Attached is HED's Preliminary Human Health Risk Assessment for the Tebuthiuron Tolerance Reassessment Eligibility Decision (TRED). This document addresses tolerances subject to reassessment in accordance with Federal Food Drug & Cosmetic Act (FFDCA) as amended by the Food Quality Protection Act of 1996 (FQPA). The FQPA requires EPA to re-evaluate existing tolerances to ensure that children and other sensitive subpopulations are protected from pesticide risks. Because FQPA addresses only non-occupational (residential) risk concerns for food-use pesticides with established tolerances or exemptions, risks to workers are not addressed in this document.

The human health risk findings summarized in this assessment incorporate disciplinary chapters and other supporting documentation as follows:

TRED for Tebuthiuron. M. Corbin (11/28/01; D279066)
Addendum to TRED Drinking Water Assessment for Tebuthiuron. M. Corbin (2/22/02; D279066)
Product Chemistry Chapter for the TRED. K. Dockter (11/15/01; D277104)
Residue Chemistry Chapter for the TRED. S. Piper (04/09/02; D277103)
Acute and Chronic Dietary Exposure Assessments for the TRED. S. Piper (04/03/02; D281821)
Toxicology Chapter for the TRED. R. Fricke (3/20/02; D277101; TXR 0050572)

Third Report of the HIARC Committee. R. Fricke (4/16/02; TXR 0050672)
Report of the FQPA Safety Factor Committee. Carol Christensen (2/12/02; TXR 0050466)
The Outcome of the HED MARC Meeting (2/25/02; TXR 0050409)

RDI: Team (04/03/02), BRSrSci: Nielsen (04/22/02), RARC (04/03/02)
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Tebuthiuron (PC Code 105501)
Preliminary Human Health Risk Assessment
HED Chapter for the Tolerance Reassessment Eligibility Decision (TRED)

1.0 EXECUTIVE SUMMARY

The following human health risk assessment has been prepared by the Health Effects Division (HED) for Phase 1 (Registrant Error Correction) of the tolerance reassessment eligibility decision (TRED) process for tebuthiuron. The Tebuthiuron Reregistration Standard Guidance Document was issued 6/94.

Tebuthiuron is a non-selective substituted urea herbicide. The mechanism of herbicidal action is the inhibition of photosynthesis. Unlike other substituted ureas such as fluometuron, diuron, and linuron, tebuthiuron contains a dimethyl thiadiazole moiety and does not degrade or metabolize to 3,4-dichloroaniline. Tebuthiuron controls broadleaf and grassy weeds and woody plants. Use sites include pastureland/rangeland, non-crop industrial areas such as highways, fence rows, firebreaks, utility rights-of-ways, railroad rights-of-ways, and clearings for wildlife habitat. Pastureland/rangeland in TX, OK and NM is the primary use site. End-use formulations include granular, pelleted/tablets, and wettable powder products which are applied using ground and aerial equipment.

The only source of dietary (food) exposure is the consumption of secondary residues in meat and milk from livestock fed tebuthiuron-treated grass forage and hay. Tolerances in meat and milk are established at 2 ppm and in grass forage and hay at 10 ppm for residues of tebuthiuron and its metabolites containing the dimethyl thiadiazole moiety. There are no registered residential uses.

Hazard Profile, Dose/Response Analysis, and FQPA Considerations

The toxicology database for tebuthiuron is not complete, but provides sufficient information to adequately identify hazards for risk assessment purposes. The acute toxicity studies indicate that tebuthiuron is more toxic for oral (Category II) exposure than for either dermal (Category IV) or inhalation (Category III) exposure. Tebuthiuron is not an eye or skin irritant and not a skin sensitizer. In a 21-day dermal toxicity study in rabbits, no dermal or systemic toxicity was observed at the limit dose of 1000 mg/kg/day. In subchronic and chronic toxicity studies in the rat the most consistent toxicological effect was decreased body weight; however, histopathological changes in the pancreas were also observed. In subchronic and chronic toxicity studies in the dog, anorexia, decreased body weight, clinical chemistry effects, and increased organ weights were observed. There was no qualitative/quantitative evidence of increased susceptibility in rat developmental and reproduction studies; however susceptibility could not as assessed in the rabbit.

The classification of tebuthiuron as a Group D, not classifiable as to human carcinogenicity, was reevaluated by HIARC. At the doses tested, neither the rat nor mouse showed any treatment-related increase in the incidence of neoplasms; however, the HIARC concluded that the dose levels were too low to assess the carcinogenic potential of tebuthiuron. Tebuthiuron was not mutagenic in bacteria, but was weakly positive for gene mutations in cultured mouse lymphoma sells. The effect in mammalian cells was, however, confined to non-activated test conditions. There was also some evidence of a clastogenic response at cytotoxic doses both with and without S9 activation. Since an acceptable *in vivo* bone marrow cytogenetic assay is not available, final conclusions regarding the mutagenic potential of tebuthiuron can not be made at this time. HED has requested new carcinogenicity studies in rats and mice and an *in vivo* mammalian bone marrow chromosomal aberration test as confirmatory data.

A dose level of 25 mg/kg/day was selected for acute dietary risk assessment based on increased post-implantation loss and fetal/litter resorptions observed at 50 mg/kg/day in the rabbit developmental study. A dose level of 14 mg/kg/day was selected for chronic dietary risk assessment based on decreased body weight and feed consumption observed at 30 mg/kg/day in F1 females in a 2-generation rat reproduction study. An uncertainty factor (UF) of 100 was applied to all doses selected for risk assessment purposes to account for interspecies extrapolation (10x) and intraspecies variability (10x).

The FQPA Safety Factor Committee recommended that the FQPA Safety Factor be reduced to 3x when assessing acute dietary exposure to females 13-50 years old because there is a data gap for the susceptibility of fetuses following *in utero* exposure to tebuthiuron. The Committee also recommended that the safety factor be removed (1x) when assessing chronic dietary exposure to the general U.S. population and all population subgroups.

Exposure and Risk Contributions from the Food Pathway

HED did not identify any risk concerns from exposure to tebuthiuron in food. The acute and chronic dietary risk estimates associated with the use of tebuthiuron do not exceed HED's level of concern ($\geq$100%) for any population subgroup. A Tier 2 deterministic chronic dietary assessment was conducted using the Dietary Exposure Evaluation Model (DEEM™) which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. Inputs to the dietary analysis included anticipated residues (ARs) from field trials and livestock feeding studies. Maximum and weighted average estimates of percent crop treated were incorporated into the acute and chronic assessments, respectively. The calculated chronic dietary exposure (residue x consumption) was compared to a chronic population adjusted dose (cPAD) of 0.14 mg/kg/day, which reflects a FQPA factor of 1x for the general U.S. population and all population subgroups. The chronic dietary exposure estimate for the general U.S. population and all subgroups was <1% of the cPAD. The acute dietary exposure was compared to an acute population adjusted dose (aPAD) of 0.083 mg/kg/day. The acute dietary risk estimates associated with the use of tebuthiuron do not exceed HED's level of concern for females 13-50 years old. The acute dietary risk estimate for this population subgroup is <1% of the aPAD.

Exposure and Risk Contributions from the Water Pathway

HED did not identify any acute or chronic risk concerns from exposure to tebuthiuron in drinking water. Tebuthiuron and its dimethyl thiadiazole-containing degradate (Compound 104) are persistent and mobile. The Environmental Fate and Effects Division (EFED) Tier II (PRZM/EXAMS) surface water modeling for residues of tebuthiuron and its degradate 104 using the index reservoir with the percent cropped area, predicts the 1 in 10 year peak (acute) concentration of tebuthiuron is not likely to exceed 15.5 μg/L. The 1 in 10 year annual average concentration (non-cancer chronic) of tebuthiuron is not likely to exceed 4.3 μg/L. The SCI-GROW predicted concentration of tebuthiuron and its degradate 104 in ground water is not expected to exceed 245 μg/L.

Aggregate Risk Assessments

HED did not identify any aggregate risk concerns. The aggregate acute and aggregate chronic dietary risk estimates include exposure to residues of tebuthiuron in food and water. No short-, intermediate- or long-term residential use scenarios were identified. Acute dietary (food) exposure is <1% of the aPAD for females 13-50. Chronic dietary (food) exposure is <1% of the chronic PAD for the general U.S. population and all population subgroups. The estimated acute and chronic EECs in ground and surface water are less than the drinking water levels of comparison indicating that acute and chronic aggregate exposures to tebuthiuron do not exceed HED's level of concern.

Data Gaps and Uncertainties

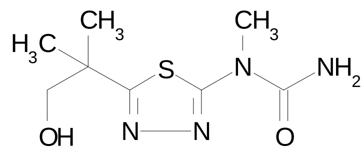
Toxicology data gaps include a developmental toxicity study in rabbit, as well as the chronic feeding/carcinogenicity study in the rat and oncogenicity study in the mouse; all of these studies were found to be unacceptable. Although tebuthiuron was not mutagenic in bacteria, it was weakly positive for gene mutations in cultured mouse lymphoma cells, but only under non-activated test conditions. An *in vivo* bone marrow cytogenetic assay is needed to fully evaluate the mutagenic potential of tebuthiuron.   Further, a 28-day inhalation study in the rat is required to characterize the effects of tebuthiuron via the inhalation route, and the requirement for a developmental neurotoxicity study is being held in reserve, pending submission of the rabbit developmental toxicity study.

The NOAEL of 14 mg/kg/day from the two-generation reproduction study used for derivation of the chronic RfD is the lowest NOAEL in the database. In other long-term toxicity studies, doses of 50 mg/kg/day (1-year dog) and 80 mg/kg/day (2-year rat) were identified as LOAELs; a LOAEL was not established in the 78-week mouse oncogenicity study at the highest dose tested (240 mg/kg/day). Based on this weight-of-evidence, the HIARC inferred that a repeat study in rats at higher dose would provide hazard characterization and evaluate the carcinogenic potential of this pesticide, but would not yield a dose that is lower than the dose that is used for derivation of the RfD. The chronic RfD is adequate to protect any adverse toxicity effects following exposure to tebuthiuron.

Although there are some uncertainties regarding the carcinogenic potential of tebuthiuron, HED has elected not to quantify cancer risk at this time because the dose levels used in the available carcinogenicity studies were sufficient to decrease any cancer risk concerns. HED has requested new carcinogenicity studies in rats and mice and an *in vivo* mammalian bone marrow chromosomal aberration test as confirmatory data.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Chemical Structure and Identification of Active Ingredient



Chemical Name:	N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea
Common Name:	Tebuthiuron
PC Code Number:	105501
CAS Registry No.:	34014-18-1
Chemical Class:	Phenylurea
Chemical Type:	Herbicide
Trade Names:	Spike
Mode of Action:	Photosynthetic inhibitor which causes disruption of cell membranes
Empirical formula:	$C_9H_{16}N_4OS$
Molecular weight:	228.3

2.2 Physical Properties

Tebuthiuron is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal. Preliminary analysis data indicate there are no impurities of toxicological concern in tebuthiuron technical material. A detailed list of the physical properties of tebuthiuron technical is provided below:

Color:	off-white
Physical state:	crystalline solid
Odor:	pungent
MP:	161.5-164C
Bulk Density:	0.579 g/cc
Water solubility:	2.5 mg/mL @25C
Vapor Pressure:	2 x 10^{-6}mm Hg @ 25C
log P_{ow}:	1.79
Stability:	Stable for 3 yrs at normal temperatures.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The toxicology database for tebuthiuron is not complete, but provides sufficient information to adequately identify hazards for risk assessment purposes. Toxicology data gaps include a developmental toxicity study in rabbit, as well as the chronic feeding/carcinogenicity study in the rat and oncogenicity study in the mouse; all of these studies were found to be unacceptable. Although tebuthiuron was not mutagenic in bacteria, it was weakly positive for gene mutations in cultured mouse lymphoma cells, but only under non-activated test conditions.   An *in vivo* bone marrow cytogenetic assay is needed to evaluate the mutagenic potential of tebuthiuron. A 28-day inhalation study in the rat is required to characterize the effects of tebuthiuron via the inhalation route. Further, the requirement for a developmental neurotoxicity study is being held in reserve, pending submission of the rabbit developmental toxicity study.

The acute toxicity studies indicate that tebuthiuron, technical, is more toxic for oral (Toxicity Category II) exposure than for either dermal (Toxicity Category IV) or inhalation (Toxicity Category III). Tebuthiuron is not an eye or skin irritant and not a skin sensitizer.   In the 21-day dermal toxicity study in rabbits, no dermal or systemic toxicity was observed at 1000 mg/kg/day (limit dose).

Although the most consistent toxicological effect was decreased body weight, histopathological changes in the pancreas were observed in both the subchronic and chronic toxicity studies in the rat. Pancreatic acinar cells of both sexes showed vacuolation, which was described as generally slight or affecting only a few cells; males also had increased relative spleen and prostate gland weights. In a rat developmental study, however, pancreatic tissue appeared normal. Subchronic and chronic toxicity studies were available for the dog. In a subchronic study, anorexia, with resulting weight loss, and clinical chemistry effects (increased blood urea nitrogen and alkaline phosphatase) were observed at 50 mg/kg/day. In a chronic (1-year) dog study, clinical signs of toxicity (emesis anorexia, and diarrhea), decreased body weight, increased alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (males only), increased absolute and relative liver weights, and increased relative kidney (females only) and thyroid (males only) weights. Results from the rat developmental and reproductive toxicity studies indicated that there was no evidence (qualitative or quantitative) for increased susceptibility following *in utero* and/or pre-/post-natal exposure. The rabbit developmental toxicity study was found to be unacceptable; susceptibility can not be evaluated in rabbits. At the doses tested, neither the rat nor mouse showed any treatment-related increase in the incidence of neoplasms. However, the HIARC (TXR No. 0050672, April 16, 2002) concluded that the dose levels were too low to assess the carcinogenic potential of tebuthiuron. Tebuthiuron was not mutagenic in bacteria, but was weakly positive for gene mutations in cultured mouse lymphoma cells. The effect in mammalian cells was, however, confined to non-activated test conditions. There was also some evidence of a clastogenic response at cytotoxic doses both with and without S9-activation. Since an acceptable *in vivo* bone marrow cytogenetic assay is not available, final conclusions regarding the mutagenic potential of tebuthiuron can not be made at this time.

In a rat metabolism study with ^{14}C-tebuthiuron, absorption was complete; excretion was rapid in both sexes, but was delayed during the first 12 hours post-dose, indicating saturation of biotransformation or excretion. At termination, no significant amounts of residual radioactivity remained in any tissue examined, but the skin showed the highest amounts relative to other tissues. Six metabolites of tebuthiuron were identified. The major urinary metabolites were identified as hydroxylated tebuthiuron metabolites.
A summary of the findings from acute toxicity tests is presented in Table 1 and a summary of the findings from the subchronic, chronic, mutagenicity and other toxicity studies is presented in Table

2.

Table 1. Acute Toxicity of Tebuthiuron Technical

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute Oral (Rat)	40583901	LD50 =477.5 mg/kg (♂♂) 387.5 mg/kg (♀♀)	II
870.1200	Acute Dermal (Rabbit)	40583902	LD50 => 5000 mg/kg (♂♂and ♀♀)	IV
870.1300	Acute Inhalation (Rat)	00155730	LC50 = 3.696 mg/L	III
870.2400	Primary Eye Irritation	40583903	Slight irritation	IV
870.2500	Primary Skin Irritation	40583902	Non-irritating	IV
870.2600	Dermal Sensitization	40583904	Non-sensitizer	–

Table 2. Subchronic, Chronic, and Other Toxicity Table		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity-rat	00020662 (1972) Acceptable/Guideline 0, 20, 50, 125 mg/kg/day	NOAEL = 50 mg/kg/day LOAEL = 125 mg/kg/day, based on decreased body weight, increased relative liver, kidney, gonads, spleen (males only), and prostate and slight vacuolization of pancreatic acinar cells.
870.3150 90-Day oral toxicity-dog	00020663 (1972) Acceptable/Guideline 0, 12.5, 25, 50 mg/kg/day	NOAEL = 25 mg/kg/day LOAEL = 50 mg/kg/day, based on decrease in body weight and increased alkaline phosphatase activity.
870.3200 21/28-Day dermal toxicity-rabbit	00149733 (1985) 00160796 (1986) Acceptable/Guideline 0, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (limit dose)
870.4100 [83-1(b)] 1-Year Feeding Study - Dog	00146801 (1985) Acceptable/Guideline 0, 12.5, 25, 50 mg/kg/day	NOAEL= 25 mg/kg/day LOAEL = 50 mg/kg/day based on clinical signs, decreased body wt, increased ALT and ALP (males only), increased absolute and relative livers and relative thyroid wt, (males only) wt, and increased absolute liver wt.
870.4200 [83-2 (b)] Oncogenicity Study - Mouse	00020717 (1986) Unacceptable/Guideline 0, 60, 120, 240 mg/kg/day	NOAEL= 240 mg/kg/day LOAEL = Not achieved Histopathology: None observed at doses tested, doses not high enough to assess carcinogenicity.
870.4300 [83-5(a)] Combined Chronic Toxicity/ Carcinogenicity Study - Rat	00020714 (1976) 00098190 (1981) 40870101 (1988) Unacceptable/Guideline 0, 20, 40, 80 mg/kg/day	NOAEL = 40 mg/kg/day, females 80 mg/kg/day males LOAEL = 80 mg/kg/day, based on decreased terminal body weight in females; not established in males Histopathology: None observed at doses tested, doses not high enough to assess carcinogenicity.
870.3700 [83-3(a)] Developmental Toxicity Study - Rat	00020803 (1972) 40485801 (1972) Acceptable/Guideline 0, 37, 72, 110 mg/kg/day	Maternal Systemic NOAEL= 72 mg/kg/day LOAEL = 110 mg/kg/day) based on decreased body weight gains and food consumption. Developmental NOAEL = 110 mg/kg/day LOAEL = not established
870.3700 [83-3(b)] Developmental Toxicity - Rabbit	00020644 (1975) 41122401 (1989) Unacceptable/Guideline 0, 10, or 25mg/kg/day	Maternal Systemic NOAEL= 25 mg/kg/day LOAEL = not established Developmental NOAEL = 25 mg/kg/day LOAEL = not established

Table 2. Subchronic, Chronic, and Other Toxicity Table		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700 [83-3(b)] Developmental Toxicity - Rabbit (Range-finding)	40776301 (1988) 5, 10, 20, 25, 50, 100 mg/kg/day	Mated rabbits (4/group). Three animals in the 100 mg/kg/day group died or were killed moribund on GD 8-10. The percentage of early resorptions in the 25, 50, and 100 mg/kg/day groups was 68.8, 66.7 and 100%, respectively.
870.3800 [83-4] 2-Generation Reproduction - Rat	00090108 (1981) Acceptable/Guideline ♂♂ 0, 7, 14, and 26 mg/kg/day ♀♀ 7, 14, and 30 mg/kg/day,	Systemic NOAEL= 14 mg/kg/day LOAEL = 30 mg/kg/day, based on deceased in body weight and weight gain in F1 females. Parental effect levels were not established for adult male rats in this study. Reproductive NOAEL = 30 mg/kg/day LOAEL = not established Offspring NOAEL = 30 mg/kg/day LOAEL = not established
870.5100 Bacterial reverse gene mutation assay	MRID 00141691 (1984) Acceptable/Guideline	There was no increase in mutant frequency in tested bacterial strains exposed up to the limit dose (5000 μg/plate) with or without S9 activation.
870.5100 Bacterial reverse gene mutation assay	MRID 00141690 (1984) Acceptable/Non-Guideline	There was no increase in mutant frequency in any S. typhimurium or E. coli tested strain exposed to tebuthiuron (98.0%,) with or without metabolic activation. There was no evidence of induced mutant colonies over background in tested *S. typhimurium strains* and E. coli strains with or without S9 activation.
870.5300 *In vitro* mammalian cell gene mutation	MRID 00145041 (1984) Acceptable/Guideline	In a mammalian cell gene mutation assay in vitro, cultures of mouse lymphoma were exposed to Tebuthiuron (98.0%) technical at concentrations limited by cytotoxicity. Mutations were not induced at any concentration with activation. Tebuthiuron was considered weakly mutagenic but only in the absence of metabolic activation. No evidence of an increased mutant frequency was observed in the presence of metabolic activation.
870.5550 Unscheduled DNA synthesis in mammalian cell culture MRID 40750901 Acceptable/Guideline	MRID 40750901 (1988) Acceptable/Guideline	In an unscheduled DNA synthesis assay, primary rat hepatocyte cultures were exposed to Tebuthiuron (99.1%) to the limit of cytotoxicity (≥900 μg/mL). UDS activity was evaluated at concentrations up to 800 μg/mL and there was no evidence of induction of UDS. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.
870.5375 *In vitro* mammalian cell chromosome aberration	MRID 41134101 (1989) Acceptable/Guideline	In a mammalian chromosome aberration assay, Chinese Hamster Ovary (CHO) cell cultures were exposed to Tebuthiuron (99.08%) at concentrations limited by cytotoxicity. A significant increase in the percent of cells with aberrations was noted in nonactivated and activated cultures at cytotoxic doses. The predominant types of aberrations were chromosome and chromatid breaks. No significant increases were observed at lower concentrations; however, rare complex aberrations, such as triradials, quadriradials and complex rearrangements were noted, providing further support for clastogenicity. Positive control values were acceptable. There was evidence of an increase in structural chromosomal aberrations over background in the presence and absence of metabolic activation at cytotoxic doses.

Table 2. Subchronic, Chronic, and Other Toxicity Table		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5915 In vivo sister chromatid exchange	MRID 40750902 (1988) Acceptable/Guideline	In an in vivo cytogenetic assay measuring sister chromatid exchange (SCE) frequency in Chinese hamster bone marrow cells female Chinese hamsters (3/group) were administered single oral doses of tebuthiuron (99.1%, Lot No. 729AS7) in 10% aqueous acacia at 3000, 4000, or 5000 mg/kg. Tebuthiuron was tested up to cytotoxic concentrations. Hypoactivity was noted in all treatment groups and bone marrow cytotoxicity (as evidenced by an increase in the percent division metaphases) was observed at 5000 mg/kg. There was no increase in the number of cells containing SCEs compared to controls at any concentration of tebuthiuron tested. Cyclophosphamide (50 mg/kg) and vehicle control values were acceptable. There was no evidence of an increase in SCEs over background.
870.7485 (85-1) Metabolism Study - Rat	42711701 (1993) 43129701 (1994) Acceptable/Guideline 10 or 100 mg/kg, 1 day 10 mg/kg/day for 14 days	Terminal distribution data showed no significant amounts of residual radioactivity in any tissue examined, but the skin showed the highest amounts relative to other tissues. Excretion was rapid at both the low and high dose levels in both sexes, but was delayed during the first 12 hours post-dose, indicating saturation of biotransformation or excretion. Six metabolites of tebuthiuron were identified. The major metabolite in 0-24 hour urine of male (58.3%) and female (62.1%) rats was identified as hydroxylated tebuthiuron metabolites (109-OH and /or 104-OH). The second most abundant metabolite was identified as metabolite 106 of tebuthiuron. This comprised between 9-15% of the administered dose in 0-24 hour urine of low dose rats, and between 1-10% of the administered dose in high dose rats. Two other metabolites identified, 104/109 and 103-OH, comprised between 2-10% of the administered dose in male and female 0-24 hour urine. Feces contained minor amounts of 104-OH and 109-OH, accounting for an average of 3.5% of the administered dose.

3.2 FQPA Considerations

The HED FQPA Safety Factor Committee met on February 4, 2002 to evaluate the hazard and exposure data for tebuthiuron. The Committee recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be reduced to 3x when assessing the risk posed by this chemical for the following reasons:

- there is no indication of quantitative or qualitative increased susceptibility of rats to *in utero* exposure;

- there is no indication of quantitative or qualitative increased susceptibility of rat offspring seen in the two-generation reproductive toxicity study;

- the dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children; and

- there is a data gap for a developmental toxicity study in the rabbit.

The reduced FQPA safety factor of 3x is required when assessing acute dietary exposure to females 13-50. This is because there is a data gap for assessing susceptibility of fetuses following *in utero* exposure to tebuthiuron. When assessing chronic dietary exposure to the general population, the FQPA safety factor will be removed (1x). This is because there was no susceptibility identified in the 2-generation rat reproduction study (a long-term study).

3.3 Dose Response Assessment

On December 13, 2001, January 17, 2002, and February 12, 2002 the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database of tebuthiuron and selected the doses and toxicological endpoints summarized in Table 3 for use in risk assessments. Also included in this table is the FQPA safety factor selected by the FQPA Safety Factor Committee on February 4, 2002. This table is followed by rationales for the selection of endpoints and doses.

Table 3. Summary of Toxicological Dose and Endpoints for Tebuthiuron for Use in Human Risk Assessment			
Exposure Scenario	**Dose Used in Risk Assessment, UF[1]**	**FQPA SF and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary females 13-50 years of age	NOAEL = 25 mg/kg/day UF = 100 Acute RfD = 0.25 mg/kg/day	FQPA SF[2] =3 $aPAD = \frac{aRfD}{FQPA\ SF}$ = 0.083 mg/kg/day	Developmental Toxicity Study - Rabbit NOAEL of 25 mg/kg/day. LOAEL not established A range-finding study showed increased early resorptions at 50 mg/kg/day
Acute Dietary general population including infants and children	N/A	N/A	No appropriate effects attributed to a single exposure was identified.
Chronic Dietary all populations	NOAEL= 14 mg/kg/day UF = 100 Chronic RfD = 0.14 mg/kg/day	FQPA SF[3] = 1 $cPAD = \frac{cRfD}{FQPA\ SF}$ = 0.14 mg/kg/day	Two-generation reproduction study in the rat LOAEL = 30 mg/kg/day, based on decreased body weight and feed consumption in F1 females
Toxicological endpoints for occupational/residential exposure risk assessments were not selected since tebuthiuron is scheduled for a Tolerance Reassessment Eligibility Decision (TRED)			

1 UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose.

2 Because there is a data gap for assessing susceptibility of fetuses following *in utero* exposure a FQPA safety factor of 3x will be used.

3 Because there was no susceptibility identified in the 2-generation rat reproduction study (a long-term study) the FQPA safety factor will be removed (1x).

Acute Reference Dose (RfD) Females 13-50 years old
The HIARC considered the data of the main study and the range-finding study to establish this endpoint. In the main study, no maternal or developmental toxicity was seen at the highest dose; the NOAEL was 25 mg/kg/day (HDT). In the range-finding study, early resorptions were observed at 25 (69%), 50 (67%), and 100 (100%) mg/kg/day. Although the range-finding study indicates that 25 mg/kg/day is an effect level, this dose (25 mg/kg/day) was selected for risk assessment since there was no dose response in the observed early resorptions and because there was greater confidence in the results of the main study where no toxicity was seen at this dose (25 mg/kg/day) and thus was deemed to be an appropriate dose for risk assessment. In addition, the selection of the 25 mg/kg/day dose for risk assessment is supported by the NOAEL of 50 mg/kg/day in a rabbit developmental range-finding study with a structurally related urea (UC 77179). This chemical had a toxicity profile similar to that of tebuthiuron. At 200 mg/kg/day UC 77179 decreased body weight gain, lethality and early resorption were observed.

Acute Reference Dose (RfD) General U.S. Population
An appropriate end point attributable to a single-dose was not available in the database. The slight decrease (7%) in body weight gain seen on gestation day 16 in the rabbit study is not attributable to a single dose and no maternal toxicity was seen in the rabbit study.

It should be noted that HED considers the finding of a lower acute RfD than the chronic RfD to be an artifact of the available data. The lower acute RfD is due to the use of an additional 3x uncertainty factor for the acute assessment (due to the lack of an acceptable rabbit developmental study). HED considered the results from the chronic study with those of the acute studies and determined that the cPAD at the higher dose level is adequately protective of females 13-50 for both the chronic toxic effect (decreased body weight and feed consumption) and the acute toxic effect (increased early resorptions).

Chronic Reference Dose (RfD)
The HIARC noted that the chronic toxicity/carcinogenicity study in rats is unacceptable since at the doses tested (0, 20, 40 or 80 mg/kg/day) no treatment-related effects were seen for mortality, clinical signs or clinical pathology. Treatment had no effects on absolute body weight or body weight gains in males and there were minimal (15% reduction) changes in absolute body weights in females at termination. There were no effects on neoplastic and non-neoplastic lesions in either sex. Because of the lack of systemic toxicity, the HIARC determined that the doses tested were inadequate to assess the chronic toxicity or the carcinogenic potential of tebuthiuron. The NOAEL of 14 mg/kg/day from the two-generation reproduction study used for derivation of the chronic RfD is the lowest NOAEL in the database. In the 1-year chronic study in dog, the NOAEL was 25 mg/kg/day and the LOAEL was 50 mg/kg/day. In the 78-week carcinogenicity study in mice, the NOAEL was 240 mg/kg/day (HDT). The HIARC inferred that a repeat study in rats at higher dose would provide hazard characterization and evaluate the carcinogenic potential of this pesticide, but would not yield a dose that is lower than the dose that is used for derivation of the RfD. The chronic RfD is adequate to protect any adverse toxicity effects following exposure to tebuthiuron. The Committee therefore concluded that an additional uncertainty factor (for data gap) is not needed.

Classification of Carcinogenic Potential
The classification of tebuthiuron as a Group D, not classifiable as to human carcinogenicity, was reevaluated by HIARC. At the doses tested, neither the rat nor mouse showed any treatment-related increase in the incidence of neoplasms; however, the HIARC concluded that the dose levels were too low to assess the carcinogenic potential of tebuthiuron.

While there is evidence that other registered substituted urea compounds are mutagenic and show carcinogenic potential, a conclusive SAR analogy between these compounds and tebuthiuron cannot be drawn because tebuthiuron contains a thiadiazole moiety and the other substituted ureas do not. An unregistered sulfonamide compound (UC77179), shown to induce thyroid adenomas in rats, also bears some structural similarities to tebuthiuron. However, comparison of tebuthiuron and UC77179 genotoxicity data does not support a strong SAR analogy. Compound UC77179 caused gene mutation is an Ames assay, produced chromosomal damage in cultured Chinese Hamster Ovary (CHO) cells, and was negative in other mutagenicity tests. Tebuthiuron was not mutagenic in bacteria, but was weakly positive for gene mutations in cultured mouse lymphoma cells. There was also some evidence of a clastogenic response at cytotoxic doses both with and without S9 activation.

Although there are some uncertainties regarding the carcinogenic potential of tebuthiuron, HED has elected not to quantify cancer risk at this time because the dose levels used in the available carcinogenicity studies were sufficient to decrease any cancer risk concerns. HED has requested new carcinogenicity studies in rats and mice and an *in vivo* mammalian bone marrow chromosomal aberration test as confirmatory data.

3.4 Endocrine Disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on tebuthiuron, there was no evidence of endocrine disruptor effects. When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, tebuthiuron may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Uses

Tebuthiuron is a non-selective substituted urea herbicide that provides long-term control of annual and perennial grasses, herbaceous plants and woody brush. Use sites include pastureland/rangeland, non-crop industrial areas such as highways, fence rows firebreaks, utility rights-of-ways, railroad rights-of-ways, and clearings for wildlife habitat; there is no agricultural crop use of tebuthiuron except for range and pasture land uses. The primary use site is pastureland/rangeland in TX, OK and NM. Based on a search of OPP's REFS conducted on 22-March-2002, there are eight active Section 3 registrations for end-use products containing tebuthiuron. End-use formulations include granular, pelleted/tablets, and wettable powder products which are applied using ground and aerial equipment.

In a SMART meeting on 2-May-2001, Dow AgroSciences expressed their intention to support all currently registered uses and products of tebuthiuron. A summary of the currently registered end-use products and use sites is given in the table below:

Company	EPA Reg. No.	Formulation Class	% ai	Use Sites
Rainbow Technology Corp.	13283-18	Granular	2	Industrial areas (outdoor) Nonag rights-of-way/fencerows/hedgerows
	13283-21	Granular	1	Industrial areas (outdoor) Nonag rights-of-way/fencerows/hedgerows
SSI Maxim Company, Inc.	34913-10	Granular	5	Drainage systems Nonag uncultivated areas/soils
	34913-15	Granular	1	Nonag uncultivated areas/soils
	34913-16	Granular	2	Nonag uncultivated areas/soils
Dow AgroSciences LLC	62719-107	Wettable Powder	80	Drainage systems Nonag uncultivated areas/soils
	62719-121	Pelleted/Tableted	20	Pasture/rangeland Nonag uncultivated areas/soils
	62719-122	Pelleted/Tableted	40	Pasture/rangeland Nonag uncultivated areas/soils

The 20% and 40% P/T formulations are registered for a single broadcast application to rangeland and forage grasses by aerial or ground equipment at 0.5-4.00 lb ai/A. Tebuthiuron may be applied anytime but the recommended timing of application is prior to the resumption of active seasonal growth in the spring or before expected seasonal rainfall. The maximum recommended rate is 4.0 lb ai/A for areas receiving $\geq$20 inches average annual rainfall, or 2.0 lb ai/A for areas receiving $\leq$20 inches average annual rainfall. Application to ditches used to transport irrigation or potable water is prohibited. Treated grasses may not be cut for hay for livestock feed for one year after treatment.

4.2 Dietary Exposure/Risk Pathway

A refined acute and chronic dietary exposure assessment was conducted for tebuthiuron registered for foliar application to pastures and rangeland (secondary transfer to livestock commodities). Anticipated residues from livestock feeding studies, residue field trials, and percent crop treated data were utilized to estimate the dietary exposure to tebuthiuron in the diets of the U.S. Population (chronic) and females 13-50 years old (acute only).

4.2.1 Residue Profile

Tolerances for residues of tebuthiuron have been established for grasses and animal commodities *[40 CFR §180.390]*. These tolerances are expressed in terms of the combined residues of N-[5-(1,1diemthylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea and its metabolites containing the dimethylethyl thiadiazole moiety.

No Codex MRLs have been established or proposed for residues of tebuthiuron. Therefore, issues of compatibility with respect to U.S. tolerances and Codex MRLs do not exist.

For dietary risk assessment, the Metabolism Committee concluded that the residue of concern in plants are the parent compound and its metabolites 103, 103(OH), 104, and 109. The residue of concern in livestock commodities (fat, meat, kidney, and liver) are tebuthiuron and its metabolites 104, 106, 108, and 109; the terminal residues of concern in milk are tebuthiuron and metabolites 104, 104(OH), 106, 109, and 109(OH). MARC revisited N. Dodd’s memo, “Nature of the Residue in Milk and Bovine Tissues,” dated 6/22/89 and determined the parent compound and its metabolites 103 (OH), 104, and 109 should also be included in the risk assessment (3/28/02; MARC members C. Olinger, L. Cheng, R. Loranger and D. Nixon).

GLN 860.1300: Nature of the Residue- Plants

The qualitative nature of the residue in grasses is adequately understood. The registrant (1976; MRID 00020756) submitted a "revised" metabolism study in which a [^{14}C]tebuthiuron solution (labeled in the 5-position of the thiadiazole ring; specific activity of 16.9 uCi/mg) was applied to the surface of the soil in which 10-week old tall fescue (0.374 lb ai/A), little bluestem and indiangrass (0.75 lb ai/A.) were grown. The residues of concern are the parent compound and its metabolites 103 (OH), 104, and 109 (N. Dodd, 12/10/87).

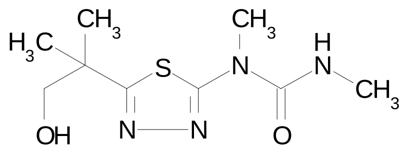
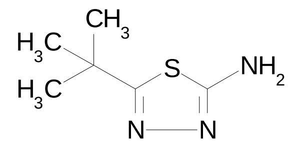
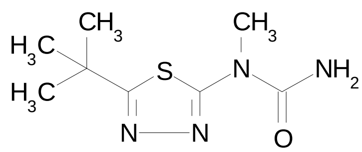
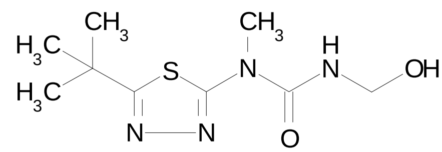
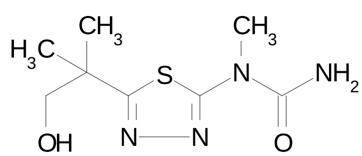
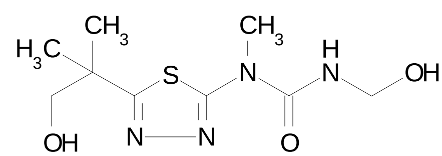
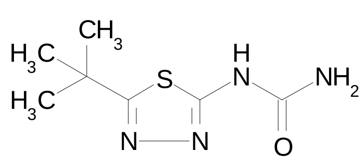
Tebuthiuron was the most abundant ^{14}C- residue recovered in the organosoluble fraction of the grass extract. Other metabolites identified in the organosoluble fraction from all three grass species were 103(OH), 104, and 109. Approximately 39-86% of the total ^{14}C-activity of all grasses was identified from the organosoluble fraction. The metabolites which were recovered and identified by acid hydrolysis of the aqueous fraction were 103(OH), 104, and l04(0H). The predominant conjugate in little bluestem was 103(OH) while 104 was the major conjugate in indiangrass. One additional metabolite, isopropyl 103, was found in the hydrolysates of the aqueous fraction of little bluestem. Based on the ^{14}C-residues identified in the organosoluble and aqueous fractions, approximately 81-89, 58-70, and 78-80% of the total ^{14}C-activity found in tall fescue, little bluestem, and indiangrass, respectively, was identified. In summary, two major metabolic pathways are involved: N-demethylation of tebuthiuron to form 104 and alkyl hydroxylation of the dimethylethyl side chain to form 103(OH). The molecular structures of the metabolites of concern are presented in Table 4.

GLN 860.1300: Nature of the Residue- Animals

The qualitative nature of the residue in milk and ruminant tissues is adequately understood. The terminal residues of concern in fat, meat, kidney, and liver are tebuthiuron and its metabolites 104, 106, 108, and 109; the terminal residues of concern in milk are tebuthiuron and metabolites 104, 104 (OH), 106, 109, and A [109 (OH)] (N. Dodd, MRIDs 40985001 and 40985002, 6/22/89). A poultry metabolism study is not required since grasses are not considered to be poultry feed items.

A metabolism study was conducted on one cow dosed by capsule containing [^{14}C]tebuthiuron labeled in the 5-position of the thiadiazole ring at a calculated feeding level of 50 ppm. Doses were administered every 12 hours (morning and evening) for 3 consecutive days. The cow was sacrificed 12 hours after the final dose. The percentage of the total radioactivity which was identified was 82.7 percent in fat, 87.2 percent in lean, 83.2 percent in liver, and 91.0 percent in kidney. The predominant residues in milk (days 1, 2, and 3) as a percentage of TRR were metabolites 104 (21%), 106 (21-26%), 104(OH) (10-16%), 109 (10-12%), and 109 (OH) (8-12%). Parent tebuthiuron was present at about 1% of the TRR.

Table 4. The chemical structures of the metabolites of concern of tebuthiuron.

Structure **Metabolite**: Chemical name	Structure **Metabolite**: Chemical name
 **103 (OH)**: N-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea	 **108**: 2-dimethylethyl-5-amino-1,3,4-thiadiazole
 **104**: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N-methylurea	 **109**: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N'-hydroxymethyl-N-methylurea
 **104 (OH)**: N-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N-methylurea	 **A [109 (OH)]**: N-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N'-hydroxymethyl-N-methylurea
 **106**: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]urea	

GLN 860.1340: Residue Analytical Methods - Plants and Animals

An adequate method is available for the enforcement of plant commodity tolerances. A GLC method with flame photometric detection is designated as Method II in PAM Vol. II. Tebuthiuron and metabolites 104 and 109 are thermally degraded on the GLC column and are determined as 5-(1,1-dimethylethyl)-N-methyl-1,3,4-thiadiazol-2-amine; metabolite 103 (OH) is determined as 5-(2-hydroxy-1,1-dimethylethyl)-N-methyl-1,3,4-thiadiazol-2-amine. The stated detection limits are 0.1 ppm for tebuthiuron and metabolites 104 and 109, and 0.2 ppm for metabolite 103 (OH). A revised enforcement method for milk, to include hydrolysis steps and the determination of metabolites 104 (OH) and A [109 (OH)], and a revised enforcement method for animal tissues, to include hydrolysis steps and the determination of metabolite 108, have been submitted.

GLN 860.1480: Magnitude of the Residue in Meat, Milk, Poultry and Eggs
The reregistration requirements for data depicting magnitude of the residue in milk, eggs, and livestock tissues are fulfilled and the data demonstrate a transfer of tebuthiuron residues to animal tissue (meat, meat by-products, etc.). An acceptable ruminant feeding study (S. Funk, D217379, 12/05/95) has been submitted. The results of the ruminant feeding study conducted at a nominal 45 ppm tebuthiuron feeding level (1.5x) for 28 days show that the existing tolerances for milk and meat are inadequate and that they should be revised. The tolerances for meat and fat may be lowered, but the tolerances for milk and meat byproducts must be increased. For details, refer to Appendix A Table 1: Tolerance Reassessment Summary for Tebuthiuron.

No poultry of swine feed items are associated with the registered uses on grass; therefore, there is no reasonable expectation of detectable residues of tebuthiuron and its metabolites in poultry, swine, and eggs resulting from the use patterns being considered for reregistration. These uses for poultry, swine, and eggs can be classified under Category 3 (no reasonable expectation of finite residues) of 40 CFR§ 180.6(a).

GLN 860.1500: Magnitude of the Residue in Plants
All data requirements for the magnitude of the residue in plants have been evaluated and deemed acceptable.

GLN 860.1520: Processed Food/Feed
No processed food/feed studies were submitted by the registrant and none are required to support the existing use pattern.

GLNs 860.1850/1900: Confined/Field Rotational Crops
Grasses in rangeland are not rotated. Pastures on the other hand can vary from permanent (>8 years), short term (2-4 years), long term (5-8 years), as well as temporary (<1 year). A rotational pasture is one used for a few seasons and then plowed and planted to another crop.

The Quantitative Usage Analysis for Tebuthiuron indicates that the states with the most acres treated are in the Southwest U.S. (TX, OK, NM, and AZ). The grassland areas covered by these states include the Southern Plains and the Southwest Grasslands. These grassland areas are predominately rangeland that contains perennial native or introduced grasses, that have been invaded by woody perennial weedy shrubs which are very difficult to control. Pastures are mostly perennial grasses or legumes; however, we do not know if there are any significant pasture acreage planted to annual forages in this region.

Therefore, confined field rotational crop studies will be conditionally required unless the registrant can provide information that pastureland in this area is either insignificant in acreage or is predominantly perennial grasses that are not rotated annually.

4.2.2 Dietary Exposure

Tebuthiuron acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.73, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and therefore represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified and noted in the risk assessment. HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys (i.e., nursing infants). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (*i.e.*, all infants or females 13-50 years old). Thus, the population subgroups listed in Table 5 include those subgroups having sufficient numbers of survey respondents in the CSFII food consumption survey.

4.2.2.1 Acute Dietary Exposure Analysis

A Tier 2 acute dietary exposure assessment was conducted for females 13-50 years old using anticipated residues for meat and milk commodities which incorporated an estimated maximum 2% CT for rangeland/pastureland (2/28/02; S. Smearman, BEAD). No acute dietary endpoint was selected by the HIARC for the general U.S. population, including infants and children. Therefore, an acute dietary exposure assessment was not performed for these population subgroups. The acute dietary exposure estimates are below HED's level of concern (≥100% aPAD) at the 95th exposure percentile for females 13-50 years old (<1% of the aPAD).

4.2.2.2 Chronic Dietary Exposure Analysis

A Tier 2 chronic dietary exposure assessment was conducted for the general U.S. population and all population subgroups (including infants and children) using anticipated residues for meat and milk commodities which incorporated an average weighted 1% CT for rangeland/pastureland provided by BEAD. The chronic dietary exposure estimates are below HED's level of concern (≥100% cPAD) for the general U.S. population (<1% of the cPAD) and all population subgroups.

Table 5. Summary of Results from Acute and Chronic DEEM™ Analyses of Tebuthiuron.

Population Subgroup	Acute Dietary[1]		Chronic Dietary[2]		Cancer Risk or MOE
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	
U.S. Population (total)	NA[3]		0.000023	<1	NA
All Infants (< 1 year)			0.000036	<1	
Children 1-6 years			0.000083	<1	
Children 7-12 years			0.000043	<1	
Females 13-50	0.000078	<1	0.000013	<1	
Males 13-19	NA		0.000025	<1	
Males 20+ years			0.000012	<1	
Seniors 55+			0.000012	<1	

1. Acute dietary endpoint applies to females 13-50 years old only. No acute dietary endpoint was chosen by the HIARC for the general U.S. population (including infants and children).
2. Chronic dietary endpoint applies to general U.S. population and all population subgroups.
3. NA - Not Applicable.

4.2.2.3 Cancer Dietary Exposure/Risk

The classification of tebuthiuron as a Group D, not classifiable as to human carcinogenicity, was reevaluated by HIARC. At the doses tested, neither the rat nor mouse showed any treatment-related increase in the incidence of neoplasms; however, the HIARC concluded that the dose levels were too low to assess the carcinogenic potential of tebuthiuron. Although there are some uncertainties regarding the carcinogenic potential of tebuthiuron, HED has elected not to quantify cancer risk at this time because the dose levels used in the available carcinogenicity studies were sufficient to decrease any cancer risk concerns. HED has requested new carcinogenicity studies in rats and mice and an *in vivo* mammalian bone marrow chromosomal aberration test as confirmatory data.

4.3 Water Exposure/Risk Pathway

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis and risk assessment for tebuthiuron. Therefore, the Agency is presently relying on computer-generated estimated environmental concentrations (EECs). PRZM/EXAMS is used to generate EECs for *surface* water and SCI-GROW (an empirical model based upon actual monitoring data collected for a number of pesticides that serve as benchmarks) predicts EECs in *ground* water. These models take into account the use patterns and the environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a screen for determining whether pesticide residues (and metabolites) in water are not of concern.

EFED (M. Corbin, 28-November-2001) provided a drinking water assessment for residues of tebuthiuron and its degradate104 that included analysis of surface and ground water monitoring data and PRZM/EXAMS (Tier II) and SCI-GROW modeling results. There is no Maximum Contaminant Level Goal (MCLG) or Maximum Contaminant Level (MCL) established by the Agency's Office of Water for tebuthiuron.

Environmental Profile:

The environmental fate database is essentially complete for parent tebuthiuron. Degradate 104 was the only tebuthiuron degradate of toxicological concern detected in the available environmental fate studies; degradate 104 was found at 6.9% of applied parent and rising by the end of the aerobic soil metabolism study. Based on the available data, the parent and degradate 104 are persistent and mobile. The quickest observed route of tebuthiuron degradation in laboratory studies was soil photolysis (half-life 39.7 days.) Tebuthiuron is stable in laboratory studies to hydrolysis, aqueous photolysis, and aerobic aquatic metabolism. Tebuthiuron was also stable during a 9-month aerobic soil metabolism study, with a calculated half-life of 35.4 months. Soil partition coefficients (Kd) from adsorption/desorption studies were 0.11, 0.62, 0.82 and 1.82, indicating that Tebuthiuron is very mobile over a range of soil types. The corresponding Koc values relating to these studies ranged from 31 to 151, with a median of 76 l/kg. The soil adsorption of Tebuthiuron appears to be related to the amount of organic carbon in the soil.

MARC Decision: The HED Metabolism Assessment Review Committee (MARC) concluded that the parent compound tebuthiuron and its degradate 104 should be included in the drinking water risk assessment. Although, MARC expressed concern about the toxicity of other metabolites of tebuthiuron, the Committee did not recommend including them in a drinking water risk assessment because they are not likely to be present in drinking water. Available data indicate that the parent and degradate 104 are persistent and mobile in the environment. Tebuthiuron is frequently detected in ground and surface water monitoring studies. The degradate 104 was detected in a retrospective ground water monitoring study and was a major degradate in a terrestrial field dissipation study accounting for up to 23% of the mass applied. The degradate 104 was also found in aerobic soil metabolism and soil photolysis studies comprising close to 7% of the mass applied. In addition, due to the structural similarity of degradate 104 to tebuthiuron (104 lacks an N-methyl group) and lack of toxicity information on degradate 104, MARC assumes that it has similar toxicity to the parent.

Estimated Environmental Concentrations:
Tier II (PRZM/EXAMS) surface water modeling for residues of tebuthiuron and its degradate 104 using the index reservoir with the percent cropped area, predicts the 1 in 10 year peak (acute) concentration of tebuthiuron is not likely to exceed 15.5 μg/L. The 1 in 10 year annual average concentration (non-cancer chronic) of tebuthiuron is not likely to exceed 4.3 μg/L. The SCI-GROW predicted concentration of tebuthiuron in ground water is not expected to exceed 245 μg/L.

Assumptions/Uncertainties for Water Exposure Pathway:

A cumulative residue approach was employed to provide conservative estimated concentrations in drinking water for tebuthiuron and its degradation products. In this approach, the fate parameters necessary for Tier II modeling are estimated from the total residue data in the available environmental fate studies. For tebuthiuron, total residue data were evaluated for the aerobic soil metabolism half life, aqueous photolysis half-life, aerobic aquatic half life, anaerobic soil metabolism half life, and hydrolysis half lives. Degradate 104 was used as a reference degradate because it was the degradate detected at the highest concentration in the environmental fate studies, is expected to be a highly mobile tebuthiuron residue in soil and aquatic environments based on its chemical structure and the fact that it was the only degradate detected in a Small Scale Retrospective Monitoring study.

Surface water concentrations of tebuthiuron were modeled using the PRZM/EXAMS (Tier II) programs for pasture/rangeland using EFED's standard scenario for alfalfa in Texas. The alfalfa scenario was chosen because its hydrologic and agronomic practices are expected to approximate those of pasture/rangeland. Groundwater concentrations were modeled using the SCI-GROW program.

4.4 Residential Exposure/Risk Pathway

An assessment of residential exposure/risk was not conducted because the registered use sites are limited to pastureland/rangeland, non-crop areas, railroad/utility rights-of-way.

4.4.1 Other Non-Occupational Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATIONS

An aggregate exposure risk assessment was performed for acute and chronic dietary (food + drinking water) exposures. Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate the chronic DWLOCs, the chronic dietary exposure estimates from food (from DEEM™) were subtracted from the cPAD value to obtain the allowable average exposure to tebuthiuron in drinking water. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (adult male and U.S. Population), 60 kg/2L (adult female), and 10kg/1L (infant & children).

DWLOCs are compared to EECs for a pesticide in surface water and ground water. If the DWLOCs are greater than the EECs, HED concludes with reasonable certainty that estimates of aggregate risks are below HED's level of concern.

5.1 Acute Risk

5.1.1 Aggregate Acute Risk Assessment

Acute aggregate risk estimates for tebuthiuron do not exceed HED's level of concern. This acute aggregate risk assessment addresses potential exposure from the combined residues of tebuthiuron and its metabolites containing the dimethylethyl thiadiazole moiety in food and residues of tebuthiuron and degradate 104 in drinking water (both surface and ground water).

5.1.2 Acute DWLOC Calculations

As shown in Table 6 below, EFED's EECs are less than the Agency's back calculated DWLOC values for tebuthiuron and its degradate 104.

Table 6. Acute DWLOC Calculations

Population Subgroup	Acute Scenario					
	aPAD mg/kg/day	Acute Food Exp mg/kg/day	Max Acute Water Exp mg/kg/day[1]	Ground Water EEC (ppb) [2]	Surface Water EEC (ppb)[2]	Acute DWLOC (µg/L)[3]
Females 13-50	0.083	0.000078	0.082922	245	15.1	2500

[1]Maximum Acute Water Exposure (mg/kg/day) = [aPAD (mg/kg/day) - acute food exposure (mg/kg/day)]
[2]Texas-grown alfalfa was selected to represent pasture/rangeland as the scenario with the highest runoff potential.
[3] Acute DWLOC(µg/L) = $\frac{\text{[maximum acute water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

5.2 Short- and Intermediate-Term Risk

The are no currently registered residential uses for tebuthiuron. Therefore, aggregate short- and intermediate-term risk assessments were not conducted.

5.3 Chronic Risk

5.3.1 Aggregate Chronic Risk Assessment

Chronic aggregate risk estimates do not exceed HED's level of concern. The aggregate chronic dietary risk estimates include exposure to residues of tebuthiuron and its metabolites containing the dimethylethyl thiadiazole moiety in food and residues of tebuthiuron and degradate 104 in drinking water (both surface and ground water). No chronic residential use scenarios were identified. Exposure (food only) to residues of tebuthiuron, based on a Tier 3 refinement using average residues from livestock feeding studies and percent of crop treated data, represent less than 1% of the chronic PAD for the general U.S. population and all population subgroups.

5.3.2 Chronic DWLOC Calculations

The EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to tebuthiuron. The EEC values used for comparison to the DWLOC are 4.31 (surface water) and 245 ppb (ground water). These estimated environmental concentrations are less than 1400 ppb which is HED's lowest drinking water level of comparison for exposure to tebuthiuron in drinking water as a contribution to aggregate chronic dietary risk. Based on the available information, HED concludes with reasonable certainty that no harm to any population will result from aggregate chronic dietary exposure to tebuthiuron. Details are presented in Table 7.

Table 7. Chronic DWLOC Calculations

Population Subgroup	Chronic Scenario					
	cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[1]	Ground Water EEC (ppb)[2]	Surface Water EEC (ppb)[2]	Chronic DWLOC (µg/L)[3]
U.S. Population	0.14	0.000023	0.139977	245	4.31	4900
All Infants (<1yr)	0.14	0.000036	0.139964	245	4.31	1400
Children 1-6 years	0.14	0.000083	0.139917	245	4.31	1400
Children 7-12 yrs	0.14	0.000043	0.139957	245	4.31	1400
Females 13+	0.14	0.000013	0.139987	245	4.31	4200
Males 13-19 years	0.14	0.000025	0.139975	245	4.31	4900
Males 20+ years	0.14	0.000012	0.139988	245	4.31	4900

Table 7. Chronic DWLOC Calculations						
Population Subgroup	Chronic Scenario					
	cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[1]	Ground Water EEC (ppb)[2]	Surface Water EEC (ppb)[2]	Chronic DWLOC (μg/L)[3]
Seniors 55+ years	0.14	0.000012	0.139988	245	4.31	4900

[1]Maximum Chronic Water Exposure (mg/kg/day) = [cPAD (mg/kg/day) - chronic food exposure (mg/kg/day)]
[2]Texas-grown alfalfa was selected to represent pasture/rangeland as the scenario with the highest runoff potential.
[3]Chronic DWLOC(μg/L) = $\frac{\text{[maximum chronic water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/μg]}}$

6.0 CUMULATIVE

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this tolerance reassessment review for tebuthiuron because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of tebuthiuron. For purposes of this tolerance reassessment review, EPA has assumed that tebuthiuron does not have a common mechanism of toxicity with other substances.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether tebuthiuron shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for tebuthiuron need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with tebuthiuron, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at:

`http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf`

In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE

Because FQPA addresses only non-occupational (residential) risk concerns, risks to occupational workers are not addressed in this document.

8.0 DATA NEEDS/LABEL REQUIREMENTS

Toxicology

OPPTS 870.3465: 28-Day inhalation toxicity study
OPPTS 870.3700b: Developmental Toxicity (non-rodent)
OPPTS 870.4100a: Chronic Toxicity (Rodent)
OPPTS 870.4200a: Oncogenicity (Rat)
OPPTS 870.4200b: Oncogenicity (Mouse)
OPPTS 870.4300: Chronic/Oncogenicity
OPPTS 870.5385: Mutagenicity- Mammalian bone marrow chromosomal aberration test
OPPTS 870.6300: Developmental Neurotoxicity (held in reserve pending submission of a rabbit developmental toxicity study)

Residue Chemistry

OPPTS 860.1340	Residue Analytical Methods: Enforcement methods for milk and animal tissues have been proposed; independent laboratory validation is required.
OPPTS 860.1850	Rotational Crops (Confined): The confined rotational crop studies are required unless the registrant can provide information that pastureland in TX, OK, and NM is either insignificant in acreage or is predominantly perennial grasses that are not rotated annually.
OPPTS 860.1100	Directions for Use: The current labels indicate that treated grasses may not be cut for hay for livestock feed for one year after treatment. The Agency considers restrictions against the grazing of treated rangeland to be impractical. Removal of this label restriction is required.

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Appendix A Table 1:   Tolerance Reassessment Summary for Tebuthiuron

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Correct Commodity Definition
Cattle, fat	2	1	
Cattle, mbyp	2	5	
Cattle, meat	2	1	
Goats, fat	2	1	
Goats, mbyp	2	5	
Goats, meat	2	1	
Grass, hay	20	10	
Grass, rangeland, forage	20	10	Grass, forage
Horses, fat	2	1	
Horses, mbyp	2	5	
Horses, meat	2	1	
Milk	0.3	0.8	
Sheep, fat	2	1	
Sheep, mbyp	2	5	
Sheep, meat	2	1	

HED recommends that the 40 CFR tolerance expression under §180.390 be modified as follows:

§ 180.390 Tebuthiuron; tolerances for residues

(a) Tolerances are established for the combined residues of the herbicide tebuthiuron (*N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl-*N*,*N′*-dimethylurea) and its metabolites *N*-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N*,*N′*-dimethylurea, *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N*-methylurea, and *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N′*-hydroxymethyl-*N*-methylurea in or on the following agricultural commodities:

Commodity	Parts per million
Grass, hay	10
Grass, forage	10

(b) Tolerances are established for the combined residues of the herbicide tebuthiuron (*N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl-*N*,*N′*-dimethylurea) and its metabolites *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N*-methylurea, –[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]urea, 2-dimethylethyl-5-amino-1,3,4-thiadiazole, and *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N′*-hydroxymethyl-*N*-methylurea in or on the following raw agricultural commodities:

Commodity	Parts per million
Cattle, fat	1
Cattle, mbyp	5
Cattle, meat	1
Goats, fat	1
Goats, mbyp	5
Goats, meat	1
Horses, fat	1
Horses, mbyp	5
Horses, meat	1
Sheep, fat	1
Sheep, mbyp	5
Sheep, meat	1

(c) A tolerance is established for the combined residues of the herbicide tebuthiuron (*N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl-*N*,*N′*-dimethylurea) and its metabolites *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N*-methylurea, *N*-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N*-methylurea, *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]urea, *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N′*-hydroxymethyl-*N*-dimethylurea, and *N*-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N′*-hydroxymethyl-*N*-methylurea in or on the following raw agricultural commodity:

Commodity	Parts per million
Milk	0.8